UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,081	04/15/2004	Norihiro Kimoto	SHZ-021	1335

959 7590 09/12/2005

LAHIVE & COCKFIELD, LLP.
28 STATE STREET
BOSTON, MA 02109

EXAMINER	
GEBREYESUS, KAGNEW H	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/826,081	KIMOTO ET AL.	
	Examiner	Art Unit	
	Kagnew H. Gebreyesus	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) *11, 12,13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. JP 2003-113402, filed on 04/17/2003. Claims 1-13 are present for examination.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7, 11 are rejected under 35 U.S.C. 101 because the claimed inventions are directed to non-statutory subject matter. In the absence of the hand of man, naturally occurring proteins and/or nucleic acids are considered non-statutory subject matter. *Diamond and Chakrabarty*, 206 USPQ 193 (1980). This rejection may be overcome by amending the claims to contain wording such as " An isolated and purified carbonyl reductase (for claims 1-4, 7, 11) and an isolated and purified polynucleotide" (for claims 5-6). For examination purposes the claim is read as such.

Claim Objections

2. Claims 12 and 13 are objected to because of the following informalities: Claims 12 and 13 are objected to for reciting "any one of claim 1 to" which should read as "claim 1".

3. Claim 11 is objected to for the typographical error reciting " at least 80%ee". Appropriate corrections are required.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 11 and dependent claims 7 and 8 are indefinite in the recitation of a "stringent conditions" as the specification does not define what conditions constitute "stringent". While page 12 of the specification describes some conditions which are intended to be stringent, there is nothing to suggest that other conditions would not also be included within the scope of this term and in the art what is considered stringent varies widely depending on the individual situation as well as the person making the determination. As such it is unclear how homologous to the sequence of a gene encoding SEQ ID NO: 1, a sequence must be to be included within the scope of these claims.

Claims 1, 2, 6 and 11 are rejected for the recitation "reductase comprising physicochemical properties" is unclear since proteins do not comprise physicochemical properties. It is suggested that applicants amend this recitation as "reductase having physicochemical properties".

Claim 2 is rejected for the recitation 38,000 without a unit. For examination purposes it will be read as 38,000 daltons (38KD).

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of carbonyl reductase polypeptide molecules from any source (claims 1 and 2) or any carbonyl reductase polypeptide from all species of *Torulaspora* (claim 3) or any carbonyl reductase polypeptide from *Torulaspora delbrueckii* defined by the activity of reducing 3, 4-dimethoxyphenylacetone and lacking (S)-1-(3,4-dimethoxyphenyl)-2-propanol oxidizing activity. The specification teaches the structure of only a few representative species of such a polypeptide. Moreover, the specification fails to describe any other representative species by any identifying structural characteristics or properties other than the functionality of encoding a enzyme with an activity of reducing 3, 4-dimethoxyphenylacetone and lacking (S)-1-(3,4-dimethoxyphenyl)-2-propanol oxidizing activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the full scope of the claimed invention.

Claims 1, 2, 3, 6-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a carbonyl reductase from *Torulaspora delbrueckii* (SEQ ID NO: 2) encoded by the polynucleotide sequence of SEQ ID NO: 1 and the polynucleotide sequences of SEQ ID NOS: 17, 21 and 25 having the activity of reducing 3, 4-dimethoxyphenylacetone and lacking (S)-1-(3,4-dimethoxyphenyl)-2-propanol oxidizing activity does not reasonably provide enablement polypeptide from any source having said

activity of reducing 3, 4-dimethoxyphenylacetone and lacking (S)-1-(3,4-dimethoxyphenyl)-2-propanol oxidizing activity or does not enable for any polynucleotide with 70% or more sequence identity to SEQ ID NO: 1 or a sequence that hybridizes to SEQ ID NO: 1. In addition the scope of the disclosure does not provide enablement to a polynucleotide sequence having one or more deletions, substitutions additions or insertions to the polynucleotide sequences of SEQ ID Nos: 17, 21 or 25 or provide enablement for a method of production of any optically active alcohol (claim 12) using any carbonyl reductase having the limitation having an activity of reducing 3, 4-dimethoxyphenylacetone and lacking (S)-1-(3,4-dimethoxyphenyl)-2-propanol oxidizing activity.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1, 2, 3, 6-13 are so broad as to encompass any polynucleotide sequence encoding a carbonyl reductase polypeptide having an activity of reducing 3, 4-dimethoxyphenylacetone and lacking (S)-1-(3,4-dimethoxyphenyl)-2-propanol oxidizing activity from any source (claim 1 and 2) or from any species of *Torulaspora* (claim 3) or any polynucleotide encoding a polypeptide with only 70% or more sequence identity to SEQ ID NO: 2 or any polynucleotide that hybridizes under stringent condition to the polynucleotide sequence of SEQ ID NO: 1. In addition claim 11 is drawn to any polypeptide encoded by a polynucleotide of SEQ ID Nos: 17, 21 and 25 wherein a deletion, substitution insertion or addition has been made at one or more positions. Claim 12 is drawn to a method of producing any optically active alcohol using a

polypeptide having an activity of reducing 3, 4-dimethoxyphenylacetone and lacking (S)-1-(3,4-dimethoxyphenyl)-2-propanol oxidizing activity.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides/nucleic acid sequences broadly encompassed by the claims. Since the nucleic acid sequence of a gene encoding the corresponding protein determines its structural and functional properties, predictability of which changes can be tolerated in the nucleic acid sequence and obtain the desired activity of the encoded protein requires a knowledge of and guidance with regard to which nucleotide(s) in the any of the polynucleotide sequences (SEQ ID Nos: 1, 16, 20 or 24), if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the nucleic acid structure relates to the function of the encoded protein. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of SEQ ID NO: 1/2 from *Torulaspora delbrueckii* and SEQ ID NO: 16/17, 20/21 and 24/25 from *Saccharomyces cerevisiae* and Zygo*saccharomyces* rouxii and a method of producing a specific optically active alcohol ((S)-1-(3,4-dimethoxyphenyl)-2-propanol) using the same.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within the DNA sequence where nucleic acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility of the encoded protein(s) are limited in any gene and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein

encoded by any gene to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of a carbonyl reductase gene with 70% or more identity to the reductase encoded by SEQ ID NOS: 2 or any polynucleotide that hybridizes under stringent condition to the polynucleotide sequence of SEQ ID NO: 1 or any polypeptide encoded by a polynucleotide of SEQ ID NOs: 17, 21 and 25 wherein any number of deletions, substitutions insertions or additions have been made at any position and the use of the specific carbonyl reductase(s) from *Torulaspora delbrueckii* or from *Saccharomyces cerevisiae* and Zygo*saccharomyces* rouxii to produce any alcohol because the specification does **not** establish: (A) regions of the nucleic acid structure which may be modified without effecting activity of the encoded protein; (B) the general tolerance of a polynucleotide (1, 16, 20, or 24) or encoded carbonyl reductase polypeptides, to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleotide residues in SEQ ID NO: 16, 20 or 24 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a carbonyl reductase having an activity of reducing 3, 4-dimethoxyphenylacetone and lacking (S)-1-(3,4-dimethoxyphenyl)-2-propanol oxidizing activity from any source (claim 1 and 2) or from any species of *Torulaspora* (claim 3) or any

polynucleotide encoding a polypeptide with only 70% or more sequence identity to SEQ ID NO: 2 or any polynucleotide that hybridizes under stringent condition to the polynucleotide sequence of SEQ ID NO: 1. In addition claim 11 is drawn to any polypeptide encoded by a polynucleotide of SEQ ID NOs: 17, 21 and 25 wherein a deletion, substitution insertion or addition has been made at one or more positions which reads on any carbonyl reductase from any source. Furthermore the specification does not teach a method of producing any optically active alcohol using any carbonyl reductase having the only limitation of having an activity of reducing 3, 4-dimethoxyphenylacetone and lacking (S)-1-(3,4-dimethoxyphenyl)-2-propanol oxidizing activity and Ph optimum of 5.5-6.5 and having a molecular weight of about 38KD. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of carbonyl reductase genes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

3. Claim 10 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 10 is rejected for reciting "a transformant". Applicants have not enabled the full scope of a transformant since transformants encompass transgenic plants, transgenic animals including humans. Applicants have not described how one skilled in the art would make and/or use the enormous numer of divers transformants as encompassed in the invention. Without sufficient guidance determination of

how to perform the full scope of how to make a transformant wherein a transgenic plant, a transgenic animal including humans etc., is unpredictable and the amount of experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 2, 6-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Costello et al (EP918090-A2). Costello et al describe new ketoreductase genes encoding polypeptide sequences from *Saccharomyces cerevisiae* and Zygo*saccharomyces* rouxii having 100% sequence identity to SEQ ID NO: 17, 21 and 25. These polypeptide sequences would inherently have all the properties of the polypeptide sequences of SEQ ID NO: 17, 21 and 25 thus will have the physicochemical properties of polypeptides having the activity of reducing 3, 4-dimethoxyphenylacetone and lacking (S)-1-(3,4-dimethoxyphenyl)-2-propanol oxidizing activity, have a pH optimum of 5.5-6.5 and have a molecular weight of about 38,000 as determined by SDS-PAGE and gel filtration since the size of SEQ ID NO: 17, 21 and 25 are 347 amino acids, 348 amino acids and 344 amino acids respectively. Claims 6-10 are also within the limitation of the polypeptide of Costello et al since claim (6c) recites any number of substitutions, deletions, insertions and/or additions.

Claim Rejections - 35 USC § 103

6. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-4, 6-8, 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michio Ito et al (US 5,679557). Michio Ito et al teach a process of asymmetrically reducing 1-phenyl-2-oxo-propane derivatives with microorganisms including *Torulaspora delbrueckii*. Michio Ito et al in example 140 teach a process of preparing an optically pure (S)-1-(3,4-dimethoxyphenyl)-2-propanol by a fermentation method comprising the microorganism *Torulaspora delbrueckii* or a preparation thereof (see page 9 column 1, line 60-65 and example 140 in Michio Ito et al) from which the polynucleotide and the encoded enzyme of the instant invention was derived from.

It would have been obvious for a person of skill in the art to further isolate and purify the enzyme responsible for the activity of reduction of the 3, 4-dimethoxyphenylacetone and lacking (S)-1-(3,4-dimethoxyphenyl)-2-propanol oxidizing activity, perform peptide sequencing and isolate the carboxyl reductase gene from this organism (anticipating claims from any organism that performs the desirable reaction.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnew H. Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Achutamurthy ponnathapura can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kagnew Gebreyesus PhD.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600